NEWS FROM THE SCIENTIFIC DIRECTOR, NIEHS

, 1999

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At the DIR Retreat in January the following areas of concern were identified by scientists.

Communications: 1) Improve communications regarding seminars, conferences, etc., 2) Establish an NIEHS DIR Bulletin Board; 3) Improve DIR web sites; 4) Provide comfortable setting to allow for informal interactions among DIR scientists; and 5) Implement more interactions between DIR and DERT.

- **The DIR Council made a number of recommendations for changes in the Seminar and Conference Room Scheduling System which have been implemented to avoid conflicts in future scheduling .**
- **News from the Scientific Director is published monthly and is available on the DIR web site (url:** http://dir.niehs.nih.gov/sdnews/ **DIR Council minutes are distributed to all DIR Section/Group Leaders.**
- **Improvements have been made on the DIR web site. On a continual basis, the web sites will be reviewed for content, ease of use, accessibility, etc. Any comments on web sites should be directed to Dr. Jim Selkirk.**
- **A coffee bar has been approved by Dr. Olden for the F module to allow scientists to discuss science over a cup of coffee. It is anticipated that the coffee bar would be open in the early mornings and mid afternoons. Mr. Hollmeyer from the Office of Management is currently working on this effort.**
- **Dr. Barrett and other OSD staff meet regularly with Dr. Sassaman and DERT staff. Dr. Van Houten, the Chief of the Program Analysis Branch, and Dr. Sassman will be invited to a future DIR Council to discuss future interactions between DERT and DIR. If you have specific issues regarding interactions with DERT, please submit any written comments to Dr. Barrett.**

Human Resources: 1) Processing of personnel actions; 2) Processing of appointment of foreign scientiststs; and 3) Clarification of recruitment procedures

- **These issues are currently being discussed with the Human Resources Management Branch. Future discussions are expected with the Associate Director for Management who will be arriving at NIEHS in July, 1999.**
- **Procedures for recruitment are now available on the Web (please refer to url:** http://www.niehs.nih.gov/omhrmb/procedur/toc.htm

Training: Increase continuing education for all scientists to include the use of tutorials on general, scientific topics.

- **Tutorial training at a general level for scientists will be a topic of discussion at the FY2000 DIR Retreat. The NTA has started the NTA Forum which includes general presentations of a research area.**

Building Security: Improvements have been made in access to the Building (External Card Entry Location at B) One suggestion was to include locks on individual offices; this can be accomplished by contacting Captain Bedick.

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"TIP" GRANTS FOR INDEPENDENT POSITIONS – DIR Has 3 Winners!

The Transition to Independent Positions (TIP) Program is an innovative funding mechanism that provides an early NIH commitment of up to three years of support for beginning investigators in environmental health science research. The goal of the TIP program is to enable the most talented, promising NIEHS trainees to obtain an NIH grant that can be activated when they find a tenure-track position to start their independent academic research careers.

Congratulations to the DIR trainees who were awarded the first TIP Grants. They are:

Michelle Bennett, Laboratory of Molecular Carcinogenesis, Project Title: "Genetic Susceptibility to Radiation Induced Mammary Carcinogenesis in BRCA2-Deficient and Inbred Mouse Strains." (Mentor - Roger Wiseman).

Sandi Dunn, Laboratory of Molecular Carcinogenesis, Project Title: "Insulin-like Growth Factor-1 Stimulates Cancer Invasion." (Mentor-J. Carl Barrett)

Beth Harvat, Laboratory of Pulmonary Patholbiology, Project Title: "Irreversible Growth Arrest and Squamous Differentiation." (Mentor-Anton Jetten).

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NEXT ROUND OF TIP GRANT PROPOSALS

This program is open to all NIEHS-funded NRSA Fellows and current NIEHS IRTA Fellows, Staff Fellows, Senior Staff Fellows, and Clinical Fellows who are U.S. citizens or Permanent Residents and who will have completed not less than 18 months nor more than 5 years of relevant post-doctoral research training on July 31, 1998.

Prospective NIEHS Intramural applicants are requested to submit a letter of intent indicating their name, mail drop, and a tentative research project title to Dr. Steven Akiyama at Mail Drop A2-09 or by e-mail at <akiyama@niehs.nih.gov> prior to **April 12, 1999**. The letter of intent is not required but will help in the review planning process and will also provide the OSD with a mechanism to communicate rapidly any changes that might occur in the TIP application process.

The TIP Program is anticipated to be very competitive. The two most important review criteria are (1) the applicant's potential to become a major contributor to the research relevant to NIEHS and (2) the originality, innovation, and significance of the research project. Because the extramural applicants will all have had prior success in competing for NIH funding, intramural TIP applicants are required to submit a pre-application to the Division of Intramural Research (DIR). Only those Intramural applicants approved by the DIR will be allowed to advance to the second step, which is a Research Scholar Development (K22) grant application submitted to the NIH Center for Scientific Review.

The DIR TIP pre-application is a 12-page (maximum) F32 (NRSA)-type application that must be submitted to the DIR no later than **May 21, 1999**. **It is strongly recommended that pre-applications be submitted earlier, if possible,** to allow more time to be spent on the subsequent K22 application. All pre-applications must first be cleared by the applicant's NIEHS sponsor and Laboratory/Branch Chief before submission to the Office of Research and Training, in the Office of the Scientific Director for review. Applicants will receive a summary critique along with the final notification of approval or disapproval generally within 30 days of receipt of the application, and no later than June 21.

The K22 applications are submitted on PHS Research Grant Application form, PHS 398, rev. 4/98. The deadline for the full K22 grant application to the NIH Center for Scientific Review is **July 27, 1999**. Applicants are instructed to consult the 1999 TIP Request For Applications on the DERT website at: <http://www.nih.gov/grants/guide/rfa-files/RFA-ES-99-006.htm> for all details concerning eligibility and application requirements, evaluation criteria, the PHS 398 application form, and application instructions. Questions should be directed to Dr. Steven Akiyama at <akiyama@niehs.nih.gov> or Dr. Michael Galvin at galvin@niehs.nih.gov>.

Important dates:

Letters of Intent due: **April 12, 1999**
Pre-application due: **May 21, 1999**
K22 application due to NIH: **July 27, 1999**

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CHANGE IN THE COMPOSITION OF THE DIR BOARD OF SCIENTIFIC COUNSELORS

There have been a number of recent changes in the composition of the NIEHS/DIR Board of Scientific Counselors. After several years of unparalleled Board leadership, Dr. Philip Iannaccone is stepping down to join the National Advisory Environmental Health Sciences Council. He will be sorely missed by all those in the DIR who were fortunate enough to work with him during his tenure as BSC Chair. His proposed replacement is Dr. Thea Tlsty who will be rejoining the BSC in July of this year.

In addition, three new Board members participated in the March review for the first time – Drs. Michelle Williams, Leona Samson, and Lawrence Marnett. Dr. Williams is a Harvard-trained epidemiologist with a strong background in biology who brings a unique assortment of talents to the Board. She will not only fulfill the role of a resource in epidemiology, which we do not presently have, but will also be able to provide insight into potential human connections of basic biological research. Dr. Samson is widely known as an expert in toxicology with a strong background in molecular biology. She will be particularly useful as we review the laboratories in our Environmental Toxicology Program. Dr. Marnett is an internationally renowned pharmacologist, known in particular for his many outstanding contributions to the study of prostaglandins and cyclooxygenases. Given his broad background and biological insightfulness, he should prove to be a very useful resource for the review of essentially all of our research programs.

At the October review, both Dr. Carol Greider and another yet-to-be-named new member will also be joining the Board. Dr. Greider is especially known for her combined strengths in molecular biology and genetics.

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PROFILES OF TENURE-TRACK SCIENTISTS

Traci Hall
Macromolecular Structure Group
Laboratory of Structural Biology

The Macromolecular Structure Group uses the tools of structural biology, primarily x-ray crystallography, to study the overlapping areas of embryonic development, cell signaling, and RNA-protein interactions. Many macromolecules involved in the processes of development, signaling, and RNA transactions are regulators of cell growth and differentiation. Thus fundamental knowledge about the structure and function of these macromolecules will contribute to our understanding of diseases such as cancer where environmental influences have resulted in aberrant growth and signaling and will also provide a structural framework for the design of therapeutic compounds that induce or inhibit specific signaling pathways.

The current projects in the Macromolecular Structure Group include structural studies of two types of proteins involved in post-transcriptional gene regulation and a model system for ribonucleoprotein machines. The first two projects focus on two types of proteins that are involved in regulating messenger RNA (mRNA) stability by binding to adenosine-uridine (AU)-rich elements (AREs) in the 3' untranslated regions of some mRNAs. These AREs have been shown to confer instability on the transcripts that contain them and are important players in regulating gene expression. Crystal structures of these proteins bound to AREs and follow up functional studies will identify residues important for sequence-specific RNA recognition and suggest how these proteins participate in regulating mRNA stability.

The third project focuses on a one protein-one RNA ribonucleoprotein catalyst to provide insight into complex, multicomponent ribonucleoprotein machines such as the ribosome or spliceosome. The system is the fifth intron of yeast mitochondrial cytochrome b pre-mRNA (bI5) and the protein CBP2 (cytochrome b pre-mRNA processing protein 2). The bI5 intron is a group I self-splicing intron. It contains the active site for the splicing reaction, but the protein co-factor, CBP2, assists in the reaction by holding the RNA in its active conformation. Determining the crystal structure of this simpler model system will allow the correlation of structure and function and should produce some general principles that can be applied to more complex protein-RNA systems involved in chromosome maintenance, mRNA splicing, and protein synthesis.

John O'Bryan
Receptor Tyrosine Kinase Signaling and Regulation
Laboratory of Signal Transduction

The focus of our group centers around the role of adaptor proteins in the integration of signal transduction cascades. In particular, we are interested in proteins which modulate the function of receptor tyrosine kinases (RTKs). A major target of numerous RTKs is the Shc family of adaptor proteins. This family of proteins lacks an enzymatic domain but consists entirely of modular protein:protein recognition motifs including Src homology 2 (SH2) and phosphotyrosine binding (PTB) domains. Specifically, we have identified a novel Shc protein, ShcC, which is highly restricted in its pattern of expression to the central nervous system. Expression of ShcC is induced in differentiating neurons as well as in regions of the

developing mouse brain undergoing differentiation. We are examining the role of ShcC in neural development and signaling using a combination of dominant negative proteins as well as activated forms of the protein. Although the members of the Shc family are well conserved in sequence, current evidence from our group, as well as others, suggests distinct functions of the various Shc family members and as such we are interested in understanding these activities.

In addition, our group is also studying a novel adaptor protein, intersectin, which consists of two amino-terminal Eps homology (EH) domains and 5 Src homology 3 (SH3) domains and is thought to regulate numerous signaling cascades including endocytosis. Recent data from a number of groups suggests that regulation of endocytosis is important for proper signaling by RTK as well as GPCR. In collaboration with two other groups, our lab has shown that intersectin co-localizes with clathrin and that expression of intersectin can inhibit endocytosis of the transferrin receptor. Furthermore, we have demonstrated that interectin overexpression is able to activate transcriptional pathways suggesting that intersectin also regulates gene expression. Interestingly, there is a larger isoform of intersectin which is restricted to the brain. This larger version is identical to the more widely expressed form except for a carboxy-terminal extension which encodes a classic Dbl homology and pleckstrin homology domain (DH/PH domain). This larger isoform of intersectin is thus thought to regulate Rho/Rac GTPases and may also play an important role in neural development. Further work by our group will help to elucidate the mechanism of intersectin function.

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WELCOME TO TREVOR ARCHER

Dr. Trevor Archer, an internationally recognized scientist in the fields of molecular endocrinology, chromatin structure/function, and gene transcriptional regulation, will head a research group on the regulation of chromatin structure and gene expression in the Laboratory of Reproductive and Developmental Toxicology Branch. His research involves the characterization of the mechanisms of the action of steroid receptors in gene regulation and the influence of chromatin remodeling on transcription factor binding to DNA as well as activity; the application of knowledge of chromatin structure on gene regulation to understanding hormone responsiveness in breast cancer cells; and the development and use of techniques for assessing the importance of chromatin remodeling for hormone regulation in several responsive systems. The long-term goals of Dr. Archer's research is to understand the mechanisms by which gene transcription becomes altered in response to environmental signals and in disease states and the role of chromatin structure in these events.

Fryer, C.J., Nordeen, S.K. and Archer, T.K. (1998) Antiprogestins mediate differential effects on glucocorticoid receptor remodeling of chromatin structure. J. Biol. Chem. 273:1175-1183.
Lee, H-L. and Archer, T.K. (1998) Prolonged glucocorticoid exposure dephosphorylates histone H1 and inactivates the MMTV promoter. EMBO J. 17:1454-1466.
Fryer, C.J. and Archer, T.K. (1998) Glucocorticoid receptor association with the hBRG1 complex is required for chromatin remodeling. Nature,393:88-91.
Xing, W. and Archer, T.K. (1998) Upstream stimulatory factors mediate estrogen receptor activation of the Cathepsin D promoter. Mol. Endocr. 12: 1310-1321.

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CORE FACILITY

The NIEHS DNA Sequencing Core has activated it’s new web site located on the DIR home page under the Core Facilities heading (http://dir.niehs.nih.gov/dirlmc/seqcore.htm). It can also be accessed

through the Junction home page under Scientific Resources. The site describes the functions of the core and is designed to help answer most questions related to automated sequencing. Even if you are doing manual sequencing or you have your own automated sequencer you should take a look. The site provides each investigator with the types of chemistries and kits available, catalog numbers and proper reaction conditions. Pages throughout the site provide assistance with automated sequence reaction purification, template and primer preparations as well as troubleshooting difficult templates, an electronic version of the sample sheet will soon be available. Basically, it contains all the information you would need to get started plus a whole lot more**!**

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RESEARCH FELLOWS

NIH is changing several Intramural Professional Designation Titles as follows:

Research Fellow is the new professional designation title for Visiting Associates, Visiting Scientists, Staff Fellows, and Senior Staff Fellows.

Senior Investigator is the professional designation title for principal investigators.

Investigator is the new professional designation title for tenure-track investigators.

The professional designation Staff Scientist will be used for staff scientists under Title 5 and Title 42.

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AWARD RECIPIENT

Congratulations to Dr. Thomas Kunkel, Director of the Environmental Biology Program and Chief of the Laboratory of Structural Biology for winning the 1998 Mutation Research Award for Excellence in Scientific Acheivement. Dr. Kunkel will receive this award at the 1999 Envirnomental Mutagen Society in Washington DC.